

Skin Permeability in the Newborn

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Skin permeability to drugs was assessed in the newborn infant using an in vitro method. Excised skin samples were studied in a Franz-type cell, and permeability to 0.1 M sodium salicylate was measured. Fourteen samples were studied, from infants of 25–41 weeks gestation and up to 8 days old. Gestation markedly affected skin permeability to salicylate, absorption being 10^2 – 10^3 times greater in in-

fants of 30 weeks gestation or less than in term infants. There are important implications for the high permeability of the preterm infant's skin; accidental poisoning from absorption of topically applied agents can easily occur, and the percutaneous route offers an alternative method of therapeutic drug administration. *J Invest Dermatol* 88:409–411, 1987

The full-term infant has a well-developed epidermis which possesses excellent barrier properties. By contrast, the infant who is born prematurely, particularly before 30 weeks gestation, has a thin epidermis with a poorly developed stratum corneum. Although rapid postnatal maturation of the epidermis occurs over the first 2–3 weeks of age [1], the preterm infant's skin is a poor barrier in this early neonatal period [2]. Two important effects of this are a high transepidermal water loss, leading to difficulties in fluid balance and temperature control, and absorption of topically applied agents. The latter has therapeutic and toxicologic implications. It is possible to administer drugs for systemic effect by the transdermal route (theophylline is an example [3]) and it is possible for preterm infants to be inadvertently poisoned by agents which are in contact with the skin (aniline dyes [4–6], hexachlorophene [7,8], and methylated spirits [9] are examples).

We wished to measure the effect of gestation on the permeability of the newborn infant's skin to drugs. Although this has been assessed indirectly by measurement of transepidermal water loss [2] or by the blanching response to topical phenylephrine [2,10], direct measurements have not been made. We examined the transport of sodium salicylate across samples of excised neonatal skin. Sodium salicylate was chosen because it has the appropriate physicochemical properties for absorption. The preterm infant's epidermis resembles the stripped skin of an adult with the viable epidermis exposed—this is similar to an aqueous protein gel which will not allow the passage of any lipophilic drugs that are poorly water soluble.

MATERIALS AND METHODS

Methods Samples of skin were taken from the upper abdomen at autopsy and stored for not more than 4 days at 4°C. Before use, any subcutaneous fat was removed with a scalpel, care being

taken not to damage the epidermis. The resulting full-thickness skin was clamped into a specially designed, Franz-type cell in which the diameter of skin separating the 2 compartments was less than 1 cm. The lower compartment (on the dermal side of the sample) acted as the receptor phase containing buffered saline (pH 7.40) with 0.02% sodium azide as a preservative. The upper compartment (on the stratum corneum side of the sample) was filled with 3 ml of 0.1 M sodium salicylate (pH 7.0). Both compartments were stirred and the entire apparatus was maintained at 37°C. Each study lasted for at least 50 h; 0.5-ml samples were removed from the lower compartment at intervals and replaced with the same volume of buffer solution. Samples were assayed for sodium salicylate concentrations using high-pressure liquid chromatography.

Fourteen skin samples were studied. They were obtained from infants whose gestations ranged from 25 to 41 weeks, and age at death from stillborn to 8 days. A further sample was obtained from an infant of 25 weeks gestation who died at 25 days.

Calculations A typical salicylate concentration-time profile is shown in Fig 1. There is little time lag and pseudosteady state conditions exist for the first 50 h of the study. Skin permeability to salicylate was calculated from the slope of the linear portion of the graph. Wherever possible, permeability was calculated as the mean of up to 3 determinations although the small size of the sample available in the very preterm infant sometimes made this impossible. Reproducibility among skin samples from the same subject was not particularly good, as up to a 5-fold difference could be observed (Fig 2). This difference, however, is of a different order of magnitude to the differences between samples from preterm and term infants, so that the technique is valid when applied to measurement of skin permeability in such diverse subjects.

RESULTS

Gestation markedly affected skin permeability to salicylate (Fig 3). Levels were high in the most immature infants of 30 weeks gestation or less, but lower by a factor of 10^2 – 10^3 in term infants. The correlation coefficient (0.68) is significant at the $p < 0.01$ level. The sample from the infant of 25 weeks gestation who died at the age of 25 days showed a mean value for salicylate flux of 6.5×10^{-8} mol/h/cm², closer to term values than those of preterm infants.

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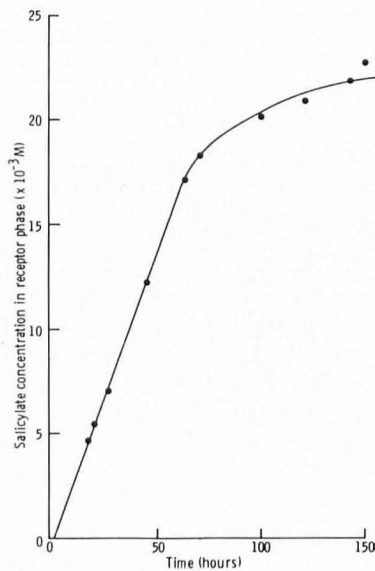


Figure 1. Concentration-time curve for salicylate absorption through excised newborn skin. There is a linear increase in salicylate concentration in the receptor phase of the Franz cell over the first 50 h. The slope of this line was used to calculate salicylate flux ($\text{mol}/\text{h}/\text{cm}^2$).

DISCUSSION

We have demonstrated that skin permeability to salicylate *in vitro* in the newborn is strongly influenced by gestation. The poorly developed epidermis of the infant born before 30 weeks gestation is more permeable to the low-molecular-weight, water-soluble drug than that of the full-term infant. Although there were not enough samples to allow the effect of postnatal age of the infant to be studied independently of gestation, the finding of a low permeability in an infant of 25 weeks gestation who survived for nearly 4 weeks supports *in vivo* work which has shown improved barrier function of the epidermis of the preterm infant outside the immediate neonatal period [2,10]. These functional changes in the epidermal barrier are closely mirrored by histologic changes [3].

The full-term infant has a well-developed epidermis. The viable epidermis is several cell layers in thickness, there is marked formation of the stratum corneum, and keratinization is prominent. By contrast, the infant born before 30 weeks gestation has an epidermis consisting of 2–3 cell layers only, a poorly defined stratum corneum, and little keratinization (Fig 4). Exposure of the skin to the extrauterine environment produces a rapid maturation of the epidermis in the early newborn period, so that by 2 weeks of age the epidermis is very similar to that of a full-term infant (Fig 5).

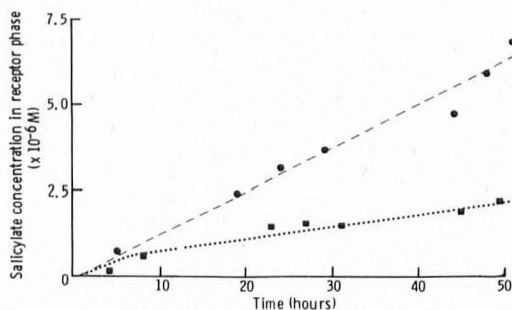


Figure 2. Linear portions of the concentration-time curve for salicylate absorption, showing results from 2 separate studies on skin taken from the same excised skin sample.

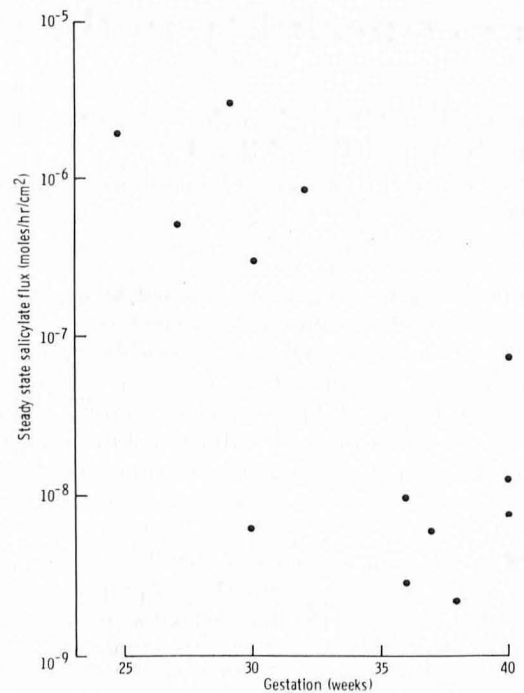


Figure 3. The effect of gestation on steady-state salicylate flux. The permeability of excised skin to salicylate is 10^2 – 10^3 times higher in infants of 30 weeks gestation or below than in term infants.

In *in vitro* studies of skin permeability, it is conventional to study isolated epidermis of known thickness from which subcutaneous fat and dermis have been removed. While subcutaneous fat was removed from the samples if present, no attempt was made to separate epidermis from dermis. The skin of the preterm infant has virtually no subcutaneous tissue, little dermis, and is extremely thin and delicate. Samples were so small that it was not possible to isolate a portion of epidermis and measure its thickness. However, epidermal thickness in abdominal skin of newborn infants has been measured elsewhere [1]. It varies from

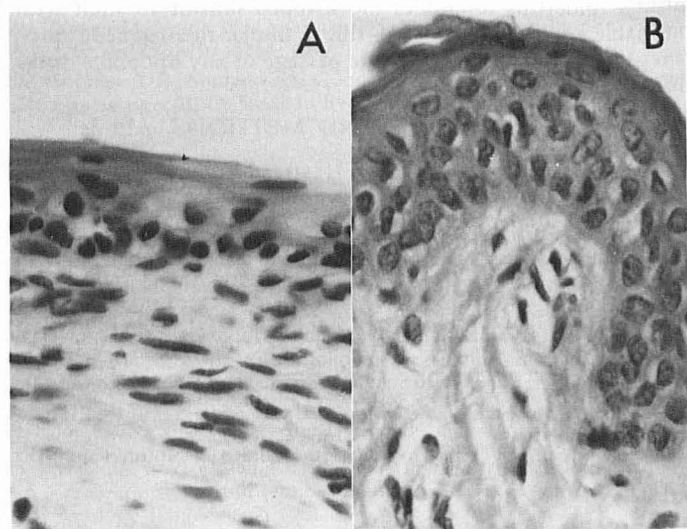


Figure 4. The effect of gestational age on epidermal development. A. Photomicrograph of a section of the abdominal skin of an infant of 26 weeks gestation, 1 day old. The epidermis is thin, with little formation of a keratinized stratum corneum. B. Similar section from a full-term infant who died during labor. The epidermis is well developed. ($\times 100$).

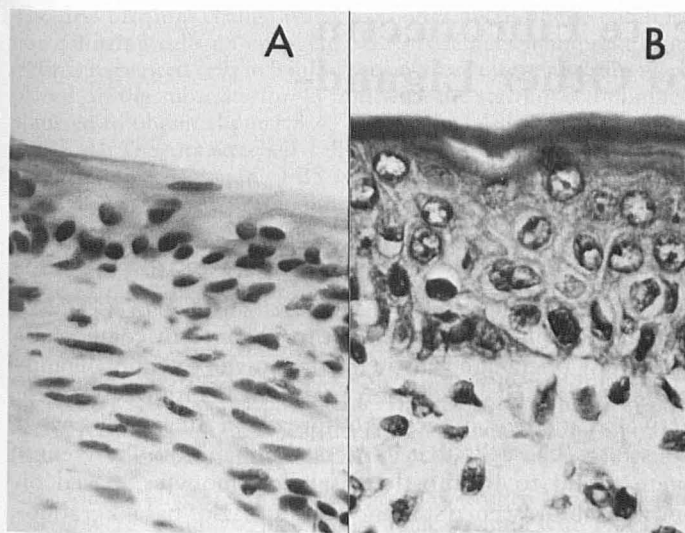


Figure 5. The effect of postnatal age on epidermal development. *A*, Photomicrograph of a section of the abdominal skin of an infant of 26 weeks gestation, 1 day old. *B*, Similar section from an infant of 26 weeks gestation, 16 days old, showing epidermal maturation similar to a term infant (Fig 4B). ($\times 100$).

approximately 20 μm before 30 weeks gestation to 50 μm at term.

This study gives further support to current thinking on drugs and the preterm infant's skin. To avoid accidental poisoning, all topically applied agents, such as antibiotics and antiseptics, should be avoided where possible or used sparingly on the very immature infant. Inadvertent poisoning from aniline dyes [4-6], hexa-

chlorophene [7,8], methylated spirits [9], and neomycin [11] have been reported. The high skin permeability, however, could be turned to the infant's advantage, allowing drugs for systemic effect to be administered transdermally. Theophylline, for example, which is commonly used to treat recurrent apnea in preterm infants, has been shown to be absorbed to therapeutic blood levels when applied to the abdominal skin [3].

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